

Amendments to the Specification:

Please add the following sentence after the title and before *FIELD OF THE INVENTION*:

--This application is a division and continuation of Ser. No. 10/212,973 filed August 6, 2002, now allowed, which is a continuation of Ser. No. 09/292,244 filed April 15, 1999.--

Please replace the text on page 2, lines 5-16, with the following rewritten text:

-- inhibits mouse skin tumors (Okuda et al., *Ibid.*). Ellagic acid has also been shown to possess anticarcinogen activity in various animal tumor models (Boukharta, M., Jalbert, G. and Castonguay, A., Efficacy of Ellagitannins and Ellagic Acid as Cancer Chemopreventive Agents – Presented at the XVIth International Conference of the Group Polyphenols, Lisbon, Portugal, July 13-16, 1992). Proanthocyanidin oligomers have been patented by the Kikkoman Corporation for use as antimutagens. The use of phenolic compounds in foods and their modulation of tumor development in experimental animal models has been recently presented at the 202nd National Meeting of the American Chemical Society (Phenolic Compounds in Foods and Their Effects on Health I, Analysis, Occurrence & Chemistry, Ho, C.-T., Lee, C.Y. and Huang, M.-T. editors, ACS Symposium Series 506, American Chemical Society, Washington, D.C. (1992); Phenolic Compounds in Foods and Their Effects on Health II. Antioxidants & Cancer ~~prevention~~ Prevention, Huang, M.-T., Ho, C.-T. and Lee, C.Y. editors, ACS Symposium Series 506, American Chemical Society, Washington, D.C. (1992)). --

Please replace the text at page 4, lines 21-27, with the following rewritten text:

-- A process for the preparation of a partially protected procyanidin dimer is provided. It comprises the steps of:

(a) protecting each phenolic hydroxyl group of a ~~procyanidin~~ catechin monomer or an epicatechin monomer with a removable protecting group which does not deactivate the A ring of the monomer, wherein the protecting step is carried out in an aprotic solvent;

(b) optionally blocking the C-8 position of the monomer of step (a) with a halo group;

(b) (c) activating for coupling the C-4 position of the compound the monomer of step (a) or step (b) by introducing an acyloxy group at the C-4 position using a lead (IV) salt of an organic acid ~~to provide an activated compound;~~ and

(e) (d) catalytically coupling the activated compound monomer of step (b) (c) with an unprotected procyanidin monomer catechin monomer or an unprotected epicatechin monomer in the presence of a coupling catalyst to produce to form the dimer.

Please replace the text at page 5, lines 7-25, with the following rewritten text:

A process is also provided for the preparation of a linear procyanidin oligomer having 4→ 8 linkages. It comprises the steps of:

(a) preparing a partially protected (4→ 8) procyanidin dimer [[,]], where the phenolic hydroxyl groups of the top mer are protected with a removable protecting group which does not deactivate the A ring of the protected mer;

(b) masking the ~~unprotected phenolic hydroxyl groups of the bottom mer~~ the dimer of step (a) to form a dimer where the phenolic hydroxyl groups of the top mer are protected, where the phenolic hydroxyl groups of the bottom mer are masked, and where the hydroxyl groups at the C-3 positions mer of both mers are masked with a removable masking group which deactivates the bottom mer;

(c) deprotecting the ~~top mer of the dimer of step (b) to provide form~~ a deprotected, masked dimer where the phenolic hydroxyl groups of the top mer are unprotected, where the phenolic hydroxyl groups of the bottom mer are masked, and where the hydroxyl groups at the C-3 positions of both mers are masked;

() catalytically coupling the dimer of step (c) with ~~an unblocked or blocked, protected, activated monomer~~ a protected catechin monomer or a protected epicatechin monomer having an acyloxy activating group at the C-4 position to form a (4→ 8) trimer where the phenolic hydroxyl groups of the top mer are protected, where the phenolic hydroxyl groups of the middle mer are unprotected, where the phenolic hydroxyl groups of the bottom mer are masked, and where the phenolic hydroxyl groups at the C-3 positions of the middle and bottom mers are masked; ~~wherein the top mer of the trimer is a protected blocked mer or a protected unblocked mer and wherein the coupling is at the C-8 position;~~

(e) masking the ~~unblocked or blocked~~ trimer of step (d) to form a trimer where the phenolic hydroxyl groups of the top mer are protected, where the phenolic hydroxyl groups of the middle mer and bottom mers are masked, and where the hydroxyl groups at the C-3 positions of all the mers are masked;

(f) deprotecting the ~~unblocked or blocked, protected, masked~~ trimer of step (e) to form ~~an unblocked or blocked masked~~ a trimer where the phenolic hydroxyl groups of the top mer are unprotected, where the phenolic hydroxyl groups of the middle and bottom mers are masked, and where the hydroxyl groups at the C-3 positions of all the mers are masked;

() catalytically coupling the trimer of step (f) with a protected catechin monomer or a protected epicatechin monomer having an acyloxy activating group at the C-4 position to form a (4→ 8) tetramer; and

(h) optionally repeating ~~or alternating steps (a) to (f) to prepare the masking, deprotecting, and coupling steps to form a higher oligomers wherein oligomer where~~ the number of mers are [[4 to 18]] 5to 18.--

Please replace the text on page 7, with the following rewritten paragraph:

--The following compounds are illustrative of a protected, masked, blocked linear trimer and a protected, masked, blocked linear trimer.--

Please delete the word “or” on page 8.

Please delete the word “or” on page 10.

Please delete the word “or” on page 12.

Please replace the sentence on page 13 with the following rewritten sentence:

--The following compounds are illustrative of compounds which result from repeating or alternating steps (a) to (f) to prepare higher oligomers wherein the number of mers is 4.--

Please delete the word "or" on page 14.

Please delete the word "or" on page 15.

Please delete the word "or" on page 16.

Please rewrite the paragraph on page 18, lines 12-17, with the following rewritten paragraph:

--The free phenolic forms of the procyanidin ~~dimer~~ dimers, linear procyanidin ~~oligomer~~ oligomers, or branched procyanidin ~~oligomer~~ oligomers are obtained by deprotecting the ~~dimer~~ dimers or ~~oligomer~~ oligomers and, if necessary, demasking and/or deblocking the ~~dimer~~ dimers or the ~~oligomer~~ oligomers. The dimers or oligomers may contain the same or different epicatechin or catechin mers. Preferably n is 5-12, more preferably n is 5. In the linear oligomers the linkages are ~~(4→6) (4→8) and/or (4→6)~~ are (4→6) or (6→4) or are (4→8) or (8→4). In the branched oligomers ~~the linkages are (4→6), (4→8, (6→4) and/or (8→4)~~ at least one of the linkages is (4→6) or (6→4) and at least one of the linkages is (4→8) or (8→4).—

Please add at page 22, after lines 18-19 the following text:

--In the following linear oligomers n is an integer from 0 to 16. --

Please delete the text on page 23 which reads:

~~linear oligomers where n is an integer from 0 to 16~~

Please replace the text on page 24 with the following rewritten paragraph:

--In the following branched oligomers, where the mers A and B are independently oligomers can be from 1 to 15, which total 3-18 with the total number of mers in the final oligomer being from 3 to 18.--

Please replace the text at page 25, lines 1-13 with the following rewritten text:

-- In the oligomers n is an integer from 2 through 18, preferably 3 through 12, more preferably 5 through 12, and most preferably 5. The oligomers have interflavan linkages of (4→ 6) and and/or (4→ 8). The oligomers prepared by the inventive process may be represented by the structures above. For the linear oligomer, when x is 0, the oligomer is termed a "dimer"; when x is 1 the oligomer is termed a "trimer"; when x is 2, the oligomer is termed a "tetramer"; when x is 3, the oligomer is termed a "pentamer"; and similar recitations may be designated for oligomers having x up to and including 16 and higher, such that when x is 16, the oligomer is termed an "octadecamer." For the branched oligomer, when ~~aA~~ B A or B is 1, the oligomer is termed a "trimer"; with similar recitations such as those described for the linear oligomers. --

Please replace the text at page 25, lines 24-28 with the following rewritten text:

-- There are multiple stereochemical linkages between position C-4 of a flavan 3-ol monomer and positions C-6 and C-8 of the adjacent monomer. The stereochemical linkages between monomeric units is designated herein as (4 α → 6) or ~~(4 β → 6)~~ or (4 β → 6) or (4 α → 8) or (4 β → 8) for linear oligomers. For linkages to a branched or junction monomer, the stereochemical linkages are (6→ 4 α) or (6→ 4 β) or (8→ 4 α) or (8→ 4 β). When (+)-catechin, designated herein as C, is linked to another C or to (-)-epicatechin, --

Please replace the paragraph on page 26, lines 3-11, with the following rewritten paragraph:

--Linear and branched oligomers can be prepared by the methods of the present invention using the steps of protecting, activating, coupling, ~~marking~~ masking, blocking, deprotecting, demasking and deblocking. In each reaction sequence the catechin or epicatechin monomers can be used to prepare linear or branched oligomers containing the same or different monomers. Higher oligomers can be prepared by repeating the coupling of a dimer, trimer, etc. with an additional catechin or epicatechin monomer using the above steps.--

Please replace the text at page 29, lines 13-23 with the following rewritten text:

-- As used herein, a “blocking group” is a removable group which directs the coupling by blocking the C-8-position of the A ring of a catechin or epicatechin monomer or a procyanidin oligomer, thus directing coupling with another procyanidin monomer to occur at the C-6 position of the A ring. The group should be removable under conditions that do not affect the procyanidin oligomer.

As used herein, a “masking group” is a removable group which masks the unprotected phenolic hydroxyl and the C-3 hydroxyl group(s) of a procyanidin monomer or higher or oligomer during the coupling of the dimer or higher oligomer with another procyanidin monomer. The group should be removable under conditions that do not affect the procyanidin oligomer.

As used herein, an “activating group” is an acyloxy group which activates the C-4 position of the C ring of a procyanidin monomer, dimer, or higher oligomer and results in coupling with another procyanidin monomer or oligomer at that position. --

Please replace the paragraph on page 30, lines 11-26, with the following rewritten paragraph:

--The protecting groups useful in this invention are electron donating moieties that function to activate ~~procyanidin~~ catechin and epicatechin monomers ~~herein below~~ at the C-4 position. In the C-4 activation reaction, electron donating phenolic protecting groups function to stabilize, and thereby assist in the formation of $[[,]]$ the intermediate C-4 benzylic cation formed by oxidation of the protected monomer with a lead (IV) salt. In the coupling reaction, an electrophilic aromatic substitution reaction, the electron donating phenolic protecting groups function again to stabilize, and thereby assist in the formation of $[[,]]$ the C-4 benzylic cation by treatment of the C-4 acyloxy substituted ~~procyanidin~~ catechin or epicatechin monomer (an activated monomer) with a Lewis acid catalyst. In the coupling reaction, the electron donating phenolic protecting groups also function to increase the differences in reactivity between the various aryl moieties that may be present in the reaction. As described below, unprotected ~~procyanidin~~ catechin or epicatechin monomers or selected ~~unprotected~~ unprotected (deprotected) monomeric units

of a procyanidin oligomer are used as nucleophiles in the coupling reaction ~~;-the~~. The C-4 acyloxy substituted, protected ~~procyanidin~~ catechin or epicatechin monomer, on treatment with a Lewis acid, functions as the electrophile. The unprotected procyanidins function as nucleophiles because they possess higher electron densities, that is higher nucleophilicities, than the protected procyanidin monomers. Any self-coupling between protected procyanidin monomers is limited due to the comparatively higher nucleophilicities of the unprotected procyanidins.--

Please replace the text at page 33, lines 17-20 with the following rewritten text:

-- In the process of this invention, the use of a coupling catalyst such as a Lewis acid (e.g. lithium ~~bromide~~ bromide) is preferred. The use of a 4 β -acetoxy derivative as the electrophile is also preferred. The selectivity of the coupling reaction is significantly improved thereby. The use of the Li⁺ as a counter ion favored C-alkylation over O-alkylation.--

Please replace the text at page 41, lines 6-9 with the following rewritten text:

-- The reagents used in the deprotection step will depend upon the group being removed. For example, when removing the benzyl protecting groups, hydrogenolysis is carried out using the conditions set forth in Examples 12, 16 and 22. When the masking groups are removed, alkaline ~~hydrolysis~~ hydrolysis is carried out using the conditions set forth in Examples 5 and 18. --

Please replace the text at page 47, lines 14-25 with the following rewritten text:

-- Tetra-*O*-benzyl-(+)-catechin (300 mg, 0.46 mmole) and lead tetraacetate (304 mg, 1.5 eq) were combined in a round bottom flask and dried under vacuum for 30 min. Argon was introduced, followed by addition of benzene and glacial acetic acid (5 mL each). The initial yellow color faded on addition of acetic acid. The solution was stirred for 24 hours at r.t. and transferred to a separatory funnel. The mixture was washed with cold 1N NaOH (4 x 50 mL), followed by water (50 mL) and finally with saturated NaCl (50 mL). The organic layer was dried over Na₂SO₄ followed by removal of solvent to

produce a brownish residue from which silica gel chromatography furnished the title compound by elution with hexane:ethyl acetate (7:3,v/v). The elute was evaporated to produce 210 mg, 66% of the ~~titled~~ title compound. ¹H NMR (CDCl₃) δ_H 7.44-7.28 (20H, m, Ar-H), 7.08 (1H, s, H-2'), 7.01, 6.95 (2H, ABq, J=8.3 Hz, H-5', H-6'), 6.41 (1H, d, J=3.6 Hz, H-4), 6.23, 6.15 (2x1H, 2xd, J=2.1 Hz, H-6, H-8), 5.16 (4H, s, CH₂Ph), 5.05, 4.97 (2x2H, 2xs, CH₂Ph), 4.83 (1H, d, J=10.3 Hz, H-2), 4.13 (1H, dd, J=3.6, 10.3 Hz, H-3), 2.23 (1H, bs, OH), 2.07 (3H, s, COCH₃). --

Please replace the text at page 49, lines 18-29 with the following rewritten text:

-- ~~4β-acetoxy~~ 4β-Acetoxy tetra-*O*-benzyl-(+)-catechin (Example 6) (140 mg, 0.2 mmol), (-)-epicatechin (290 mg, 5 eq) and LiBr (87 mg, 5 eq) were dissolved in a mixture of THF and methylene chloride (5 mL each) and the solution refluxed for 24 hours after which the solution was partitioned between ethyl acetate and water (40 mL each). The organic layer was dried over Na₂SO₄ followed by evaporation of the solvent. The residue was resuspended in ethyl acetate and filtered to remove most of the (-)-epicatechin. The filtrate was evaporated and subjected to silica gel chromatography where methylene chloride:ethyl acetate (1:1, v/v) elute furnished 116 mg, 62% dimer as an off-white powder. For the NMR spectrum the Hs comprising the upper monomer of the dimer are designated A and the Hs comprising the lower monomer of the dimer are designated B. ¹H NMR (CDCl₃:d₄-methanol, 9:1) δ_H 7.36-7.23 (20H, m, Ar-H), 7.02-6.74 (5H, m, A-5', A-6', A-2', B-2', B-5'), 6.35 (1H, dd, J=1.7, 8.2 Hz, B-6'), 6.18-6.16 (2H, ABq, J=2.2 Hz, A-6, A-8), 5.86 (1H, s, B-6), 5.12 (5H, m, CH₂Ph, B-2), 4.90 (2H, s, CH₂Ph), 4.71 (1H, d, J=8.2 Hz, A-2), 4.59 (1H, d, J=10 Hz, CH₂Ph), 4.47 (1H, d, J=10 Hz, --

Please replace the title at page 52, line 16 with the following rewritten title:

--Preparation of Tetra-*O*-benzyl-(-)-epicatechin-(4β→ 8)-(-)-epicatechin--

Please replace the text at page 53, lines 7-13 with the following rewritten text:

-- Tetra-*O*-benzyl-(-)-epicatechin-(4β→ 8)-(-)-epicatechin prepared in Example 15 (40 mg, 0.043 mmol) was dissolved in 8 mL methanol and degassed by blowing argon

for 10 min. To the solution, 25 mg of 30% palladium-charcoal was added and the mixture hydrogenolyzed at 45 psi for 3 hours. The solution was filtered through Celite followed by washing with 25 mL methanol. The combined filtrate and washing were evaporated and the residue dissolved in water. Lyophilization provided 23 mg of an off-white powder. HPLC analysis (Figure 1A) revealed the presence of 18% monomer, 45% dimer, 25% trimer and 8% tetramer. The ^1H NMR spectrum is shown in Figure 2. --

Please replace the title at page 57, line 23 with the following rewritten title:

-- Preparation of 8-Bromo ~~pentabenzyl~~penta-O-benzyl(-)-epicatechin --

Please replace the paragraph beginning at page 60, lines 17-20 with the following rewritten paragraph:

-- For instance, 8-bromo pentabenzyl(-)-epicatechin prepared by Example 26 is reacted with hexabutyl distannane to provide the alkyl stannane of pentabenzyl (-)-epicatechin. Coupling of this stannane with another 8-bromo pentabenzyl (-)-epicatechin in the presence of tetrakis (triphenyl phosphine) palladium₍₀₎ in benzene provides the ~~deca-benzyl(-)-epicatechin~~ decabenzyl(-)-epicatechin dimer with a an (8 \leftrightarrow 8) linkage. Deprotecting with H_2/Pd provides the (-)-epicatechin-(8 \leftrightarrow 8)-(-)-epicatechin in free phenolic form.--